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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/422,999	10/22/1999	HIROAKI KAWASAKI	MIT-103	6219

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EXAMINER	
MURPHY, JOSEPH F	

ART UNIT	PAPER NUMBER
1646	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/422,999	KAWASAKI ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4-7,9,11-117 and 121-130* is/are pending in the application.

4a) Of the above claim(s) *12-37,55-61,63-117 and 121-130* is/are withdrawn from consideration.

5)☒ Claim(s) *40-44,46 and 47* is/are allowed.

6)☒ Claim(s) *2, 4-7, 9, 11, 38-39, 45, 48-54, 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Comparison B* .

DETAILED ACTION

Formal Matters

Claims 118 and 120 were cancelled, claims 2, 4, 9, 11, 38, 39, 42, 43, 45 and 50-54 were amended in Paper No. 16, 2/15/2002.

Claims 2, 4-7, 9, 11-117, and 121-130 are pending. Claims 12-37, 55-61, 63-117, 121-130 are withdrawn from consideration pursuant to 37 CFR 1.142(b). Claims 2, 4-7, 9, 11, 38-54, 62 are under consideration.

Response to Amendment

The rejection of pending claims 42-45, 50-54 and 62 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention has been obviated by Applicant's amendment, and is thus withdrawn.

The rejection of claim 4 under 35 USC § 112, second paragraph has been obviated by Applicant's amendment, and is thus withdrawn.

The rejection of claims 5-7 under 35 U.S.C. 102(b) as being anticipated by Hillier et al. (1995) has been withdrawn based on Applicant's arguments.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4, 9, 11, 38-39, 45 stand rejected, and claims 50-54 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record set forth in Paper No. 11, 2/21/2001, and Paper No. 14, 7/26/2001. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The rejection of record set forth that these are genus claims because the term "variant" is defined in the specification as sequences being 70-80% similar, or 60-70% identical to a disclosed sequence. The claims also encompass nucleic acid sequences encoding "mutants" of hcAMP-GEFII protein. The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Thus, the scope of the claim includes numerous structural variants and mutants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claims provide insufficient guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general

knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 17, encoding SEQ ID NO: 18, alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Applicant argues that the claims as amended recite a function that the variants must exhibit. However, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the

species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

Because the specification fails to describe more than a single species of each genus, and because one of skill in the art could not be expected to predict the biological activity of the sequence variants and mutants encompassed by the claims, the written description requirement has not been met.

Claims 4, 5-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

These are genus claims. The claims encompass nucleic acids which hybridize under the conditions set forth in claim 4, and nucleic acids which comprise 8, 10 or 15 nucleotides of nucleotides 1-2607 of SEQ ID NO: 17. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification states that these

types of changes are routinely done in the art, the specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 17 alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claims 2, 4, 5-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid of SEQ ID NO: 17, does not reasonably provide enablement for nucleic acids which hybridize under the conditions set forth in claim 4, and nucleic acids which comprise 8, 10 or 15 nucleotides of nucleotides 1-2607 of SEQ ID NO: 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are overly broad by encompassing for nucleic acids which hybridize under the conditions set forth in claim 4, mutants of such nucleic acids, and nucleic acids which

comprise 8, 10 or 15 nucleotides of nucleotides 1-2607 of SEQ ID NO: 17, since insufficient guidance is provided as to which of the polynucleotide species encoding the myriad of polypeptide species encompassed by the claim will retain the characteristics of a hcAMP-GEFII protein. Applicants have not disclosed any actual or prophetic examples on expected performance parameters of any of the possible muteins of hcAMP-GEFII. However, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function, and even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

There is insufficient guidance provided in the specification as to how one of ordinary skill in the art would generate a nucleic acid encoding a hcAMP-GEFII polypeptide other than those exemplified in the specification. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors considered to be relevant in the instant case are set forth below:

(1) the breadth of the claims - The claims included in the instant rejection encompass nucleic acids which hybridize under the conditions set forth in claim 4, mutants of such nucleic

acids, and nucleic acids which comprise 8, 10 or 15 nucleotides of nucleotides 1-2607 of SEQ ID NO: 17

(2) the nature of the invention - The instant invention is a nucleic acid.

(3) the state of the prior art - The Voet reference demonstrate that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function.

(5) the level of predictability in the art - The Voet reference demonstrate the unpredictability of the protein art.

(6) the amount of direction provided by the inventor - Applicant has only taught one nucleic acid sequence encoding hcAMP-GEFII.

(7) the existence of working examples - Working examples are provided only for one nucleic acid sequence encoding hcAMP-GEFII.

(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Given the breadth of claims 4-7 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 38, 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Due to the limitation of "allelic variant" recited in the claim, a determination of what the claim as a whole covers indicates that elements that are not particularly described, e.g. the sequence of the claimed allelic variants, are encompassed by this claim. There is no actual reduction to practice of the claimed invention, or complete detailed description of the structure. A biomolecular sequence described only by a functional characteristic, in this case an allelic variant of a protein whose sequence is set forth in SEQ ID NO: 18, without any known or disclosed correlation between the function and the structure of the sequence is not a sufficient identifying characteristic. See University of California v. Eli Lilly and Co. 43 USPQ2d at 1406. There is no known or disclosed correlation between this function and the structure of the non-described allelic variants and the disclosed polypeptide with an amino acid sequence as set forth in SEQ ID NO: 18. Weighing all factors in view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the disclosure that the Applicant was in possession of the claimed invention.

Claim 38 and 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination

of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Due to the limitation of "gene" and "endogenous regulatory region" recited in the claims, a determination of what the claim as a whole covers indicates that elements which are not particularly described, e.g. promoters, enhancers, untranslated regions and introns, are encompassed by this claim. There is no actual reduction to practice of the claimed invention, or complete detailed description of the structure. A biomolecular sequence described only by a functional characteristic, in this case an isolated genomic nucleic acid encoding SEQ ID NO: 18, without any known or disclosed correlation between that function and the structure of the sequence is not a sufficient identifying characteristic. See University of California v. Eli Lilly and Co. 43 USPQ2d at 1406. There is no known or disclosed correlation between this function and the structure of the non-described regulatory elements and untranslated regions of the genomic DNA. Weighing all factors in view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the disclosure that the Applicant was in possession of the claimed invention.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 9, 11, 45, 48-54, 62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 and 62 are vague and indefinite because in the recitation of the term "functional domain" because it is unclear what function is to be exhibited by the domain. The guanine nucleotide exchange factor activity recited in the claim does not refer to the "functional domain".

The term "corresponding to" in claim 48 is a relative term which renders the claim indefinite. The term " corresponding to " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Claims 49-54 are rejected insofar as they depend on the recitation of the term "corresponding to".

The term "normal" in claims 2, 4, 9, 11 and 45 is a relative term that renders the claims indefinite. The term " normal " is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Claims 50-54 are rejected insofar as they depend on the recitation of the term " normal ".

The term "mutant" in claims 2, 4, 9, 11 and 45 is a relative term that renders the claims indefinite. The term "mutant" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Claims 50-54 are rejected insofar as they depend on the recitation of the term "mutant".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 4-7, 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonaldo et al. (1996).

Bonaldo et al. teach developed a method to construct directionally cloned normalized cDNA libraries and applied it to generate infant brain (INIB) and fetal liver/spleen (INFLS) libraries, from which a total of 45,192 and 86,088 expressed sequence tags, respectively, have been derived. The EST cloned by Bonaldo et al. has at least 46 consecutive nucleotides of SEQ ID NO: 17 (see Sequence Comparison B, attached) thus claims 5-7 are anticipated. This nucleotide would also hybridize to SEQ ID NO: 17 under he conditions set forth in claim 4, thus anticipating the claim. This nucleotide encodes a "mutant" or "variant" of SEQ ID NO: 17, thus claim 2 is anticipated. Claim 11 is anticipated because an antigenic determinant is only 6 amino acids, and the nucleic acid taught by Bonaldo et al. would encode a longer stretch of identical amino acids than that.

Claims 48-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Mehta et al. (1996).

Mehta et al. teaches the identification of a novel regulatory element of the human LDL receptor (Mehta at 33616). Mehta teaches the use of reporter gene expression plasmids (Mehta at 33617). These expression plasmids meet the limitations of claim 48 because the ATG of the Luc expression plasmid corresponds to an "endogenous regulatory region" of SEQ ID NO: 17. Claim 49 is anticipated because the "endogenous regulatory region" is operably linked to a marker gene, in this case the luciferase gene.

Conclusion

Claims 2, 4-7, 9, 11, 38-39, 45, 48-54, 62 are rejected.

Claims 40-44, 46-47 are allowable.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
April 16, 2002

DAVID S. ROMEO
PRIMARY EXAMINER